Nucleophilic trifluoromethylation of aziridinyl ketones: A convenient access to fluorinated aziridinyl alcohols

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Nucleophilic trifluoromethylation of aziridinyl ketones; a convenient access to fluorinated aziridinyl alcohols

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ABSTRACT

A convenient synthesis of α-(aziridin-2-yl)-α-(trifluoromethyl) alcohols starting with ethyl aziridine-2-carboxylates is reported. Grignard reaction with the corresponding Weinreb amides led to aziridin-2-yl ketones, and subsequent treatment with Ruppert-Prakash reagent gave the trimethylsilylated target compounds as mixtures of diastereoisomers, which were desilylated with TBAF. In the case of ethyl 1-((*S*)-1-phenylethyl)aziridine-2-carboxylate, (*S,S*)- and (*S,R*)-aziridin-2-yl ketones were obtained, separated chromatographically and transformed into the desired enantiomerically pure α-trifluoromethylated alcohols.

1. Introduction

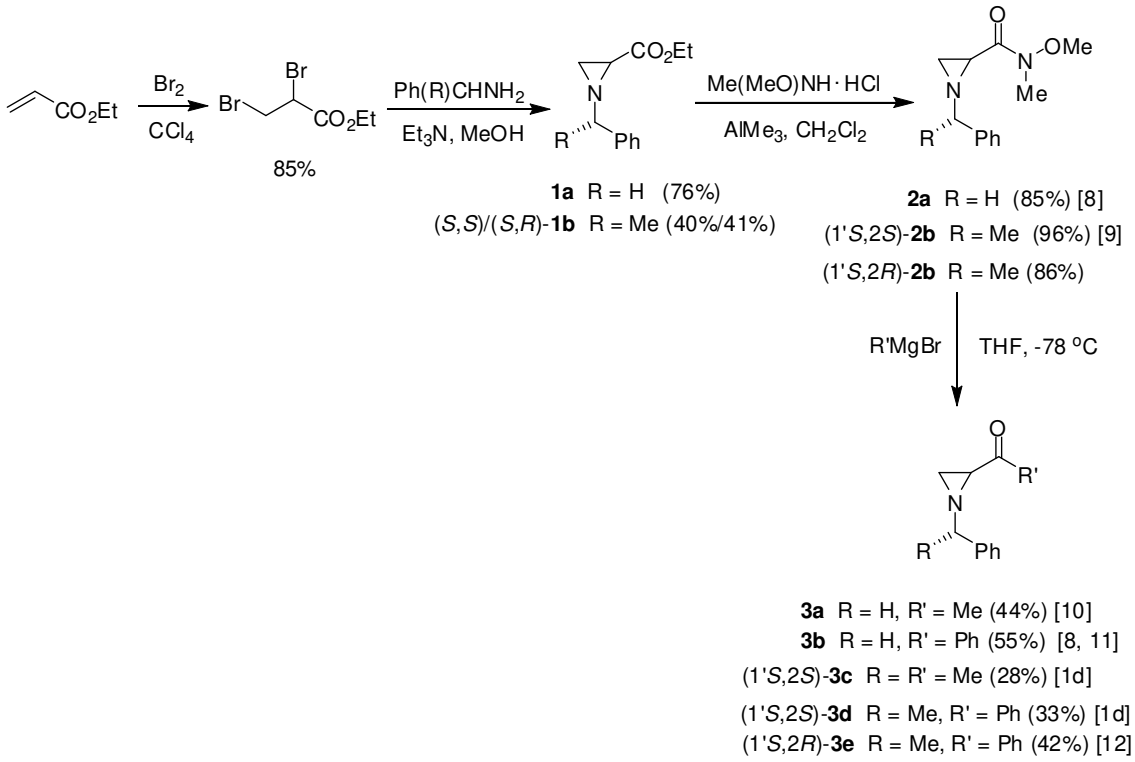
An important group of aziridine derivatives are aziridinyl alcohols. They found numerous applications as building blocks for the preparation of natural compounds [1] and drugs [2]. In addition, enantiomerically pure aziridinyl alcohols are extensively

used as a new type of potent ligands for asymmetric synthesis [3]. The introduction of fluorine atoms into a molecule of an organic compound results in significant modifications of its chemical, physicochemical and biological properties [4]. Fluorinated aziridines are rare, and to the best of our knowledge, trifluoromethylated aziridinyl alcohols are not known to date. The nucleophilic trifluoromethylation with Ruppert-Prakash reagent, i.e., (trifluoromethyl)trimethylsilane (CF_3SiMe_3), is a common procedure for the conversion of α-amino aldehydes and α-amino ketones into β-amino-α-trifluoromethyl alcohols [5], an important class of fluorinated organic compounds.

Aziridinyl ketones are attractive building blocks, which found diverse applications in the synthesis of aziridinyl-functionalized products, including aziridinyl alcohols [1a], [6]. However, they have never been explored for the preparation of fluorinated representatives. The goal of the present study was the elaboration of an efficient method for the preparation of α-(aziridin-2-yl)-α-trifluoromethyl alcohols, including enantiomerically pure examples.

2. Result and discussion

The starting aziridinyl ketones were prepared using aziridine-2-carboxylates **1** [7], which are easily available via the two-step synthesis outlined in Scheme 1. The second step, leading to the aziridine, comprises the treatment of 2,3-dibromopropanoate with benzylamine and (*S*)-α-methylbenzylamine, respectively.



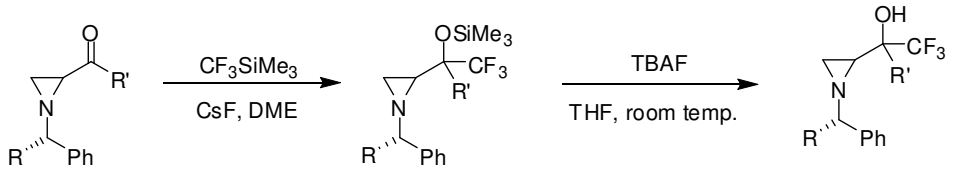
Scheme 1. Synthesis of aziridinyl ketones **3**.

In both reactions, the required aziridines were obtained in good yields. The diastereoselectivity in the case of the formation of **1b** was very low and comparable amounts of (*S,S)*- and (*S,R*)-**1b** were isolated after column chromatography.

In order to convert aziridine-2-carboxylates **1** into the corresponding aziridinyl ketones, they were transformed into their Weinreb amides **2** (*Scheme 1*) by aminolysis with methoxy(methyl)amine in dichloromethane at 10 °C [1d]. Subsequent reaction of **2** with an appropriate Grignard reagent (MeMgBr, PhMgBr), led to the corresponding aziridinyl ketones **3** [1d][10-12]. After column chromatography they were obtained as pure substances in satisfactory yields.

The nucleophilic trifluoromethylation of C=X bonds (X = O, N, S) has extensively been studied and excellent reviews related to this problem appeared in recent two decades [13]. Typically, reactions of CF_3SiMe_3 with ketones are performed in THF solution using tetrabutylammonium fluoride (TBAF) as a catalyst. However, an alternative protocol, based on the use of cesium fluoride CsF as a catalyst, without any solvent, is also known [14]. Under these conditions, α,β-unsaturated ketones are converted into trifluoromethylated alcohols in a regioselective manner [14c]. In our study, the

trifluoromethylation of ketones **3** was performed in absolute dimethoxyethane (DME) with CF_3SiMe_3 using dry CsF as a catalyst. In all cases, the silylated alcohols **4** (*Scheme 2*) were obtained as mixtures of diastereoisomers, and the *dr* values (1:1–8:2) were determined by ^{19}F NMR or ^{1}H NMR spectroscopy. The highest value was found in the case of **4b** (59%) (*Table 1*). The preliminary TLC analysis (SiO_2) of the crude mixtures showed that the isomeric products **4** differ in polarity and can be separated chromatographically. For example, in the case of the mixture **4c/4c'**, the fast (major) isomer **4c** showed $R_f = 0.22$ and the slow (minor) was detected at $R_f = 0.10$ (developed in CH_2Cl_2/pentane (1:4) mixture). Based on this observation, the mixtures of the diastereoisomeric products **4** were separated by column chromatography, and some of them were desilylated by treatment with tetrabutylammonium fluoride (TBAF) in THF solution yielding the non-protected alcohols **5** (*Scheme 2*). These products decomposed during attempted chromatography on a silica gel column, and distillation under reduced pressure was applied to obtain analytically pure samples.



3a R = H, R' = Me
3b R = H, R' = Ph
(1'*S*,2*S*)-**3c** R = R' = Me
(1'*S*,2*S*)-**3d** R = Me, R' = Ph
(1'*S*,2*R*)-**3e** R = Me, R' = Ph

4a R = H, R' = Me (fast)
4a' R = H, R' = Me (slow)
4b R = H, R' = Ph (fast)
4b' R = H, R' = Ph (slow)
(1''*S*,2'*S*,2*S*)-**4c** R = R' = Me (fast)
(1''*S*,2'*S*,2*R*)-**4c'** R = R' = Me (slow)
(1''*S*,2'*S*,1*S*)-**4d** R = Me, R' = Ph (fast)
(1''*S*,2'*S*,1*R*)-**4d'** R = Me, R' = Ph (slow)
(1''*S*,2'*R*,1*S*)-**4e** R = Me, R' = Ph (fast)
(1''*S*,2'*R*,1*R*)-**4e'** R = Me, R' = Ph (slow)

5a R = H, R' = Me
5a' R = H, R' = Me
5b R = H, R' = Ph
5b' R = H, R' = Ph
(1''*S*,2'*S*,2*S*)-**5c** R = R' = Me

(1''*S*,2'*S*,1*S*)-**5d** R = Me, R' = Ph
(1''*S*,2'*S*,1*R*)-**5d'** R = Me, R' = Ph
(1''*S*,2'*R*,1*S*)-**5e** R = Me, R' = Ph

Scheme 2. Nucleophilic trifluoromethylation of aziridinyl ketones **3** with Ruppert-Prakash reagent.

The typical protocol for desilylation of trifluoromethylated ethers **4** using aqueous hydrochloric acids [14] could not be applied as aziridine derivatives are known to undergo ring opening reaction upon treatment with strong acids [15].

Table 1. Trifluoromethylation of aziridinyl ketones **3** and desilylation of ethers **4**

Substrate	*dr* (**4**:**4'**)[a]	Yield [%]		Yield [%]
		total	**4** (fast)[b] **4'** (slow)[b]	**5** **5'**
3a	2:8	59	10	41
			49	45
3b	2:8	64	20	33
			44	24
(1'*S*,2*S*)-**3c**	6:4	49	31	71
			18[c]	-
(1'*S*,2*S*)-**3d**	5:5	64	34	28
			30	33
(1'*S*,2*R*)-**3e**	8:2	46	44	88
			2[c]	-

[a] *dr* values were determined spectroscopically (^{19}F NMR or ^{1}H NMR).

[b] 'fast' relates to the less polar fraction isolated after chromatographic separation on silica gel, and 'slow' relates to the more polar fraction, respectively.

[c] compound was isolated as a minor product contaminated with substantial amounts of appropriate isomer of fast-**4**

In the IR spectrum of **5c**, a characteristic broad absorption of the OH group was observed at 3416 cm^{-1}. In the ^{13}C NMR spectrum of **5c**, the absorptions of the aziridine C-atoms appeared at 29.8 (CH_2) and 40.8 (CH) ppm. The signal of the C-OH group was detected as a quartet with $^{2}J_{F,C}$ = 28.5 Hz at 70.0 ppm, and the CF_3 group absorbed at 125.9 ppm as a quartet with $^{1}J_{F,C}$ = 282.1 Hz. The ESI-MS showed the $[M+1]^+$ peak at *m/z* = 260, which confirms the molecular formula $C_{13}H_{16}F_3NO$.

Finally, the structure of the aziridinyl alcohol **5c**, obtained from the faster moving (TLC) trimethylsilyl-protected precursor **4c**, was established by X-ray crystallography (Figure 1). The space group permits the compound in the crystal to be enantiomerically pure, but the absolute configuration of the molecule has not been determined. The

enantiomer used in the refinement was based on the known (*S*)-configuration of the α-methylbenzyl substituent at N(1), which had been introduced into the molecule as (*S*)-α-methylbenzylamine (*Scheme 1*). On this basis, the configuration of **5c** is (*S*,*S*,*S*) [17]. The hydroxy group forms bifurcated hydrogen bonds. One is an intramolecular interaction with the N-atom forming a loop with a graph set motif [18] of S(5). The other is an intermolecular interaction with the N-atom of a neighbouring molecule, which links pairs of molecules into C_2-symmetric dimers and can be described by a graph set motif of $R^2_{,2}(10)$. Both interactions considered together form a $R^2_{,2}(4)$ loop.

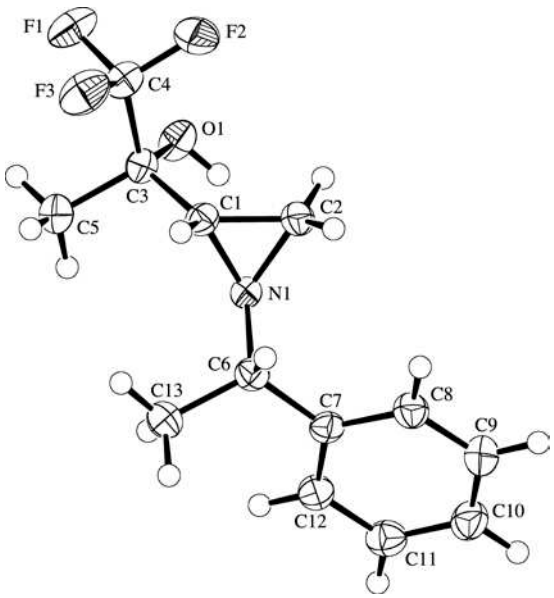


Figure 1. ORTEP Plot [16] of the molecular structure of aziridinyl alcohol (*S,S,S*)-**5c** (50% probability ellipsoids; arbitrary numbering of atoms)

3. Conclusions

The results of this study show that the nucleophilic trifluoromethylation of aziridinyl ketones using the Ruppert-Prakash reagent opens a convenient access to trifluoromethylated aziridinyl alcohols. In the case of aziridinyl ketones bearing the stereochemically defined α-methylbenzyl residue at the N-atom, the trifluoromethylation occurs diastereoselectively, with higher *dr* values in the case of the phenyl ketones. The obtained trifluoromethylated aziridinyl alcohols and their O-silylated derivatives are potentially useful, new ligands for asymmetric synthesis. Moreover, due to the usefulness of aziridines in the synthesis of more complex

heterocycles [19], products **4** and **5** can be considered as attractive building blocks for the preparation of fluorinated heterocycles.

4. Experimental part

4.1. General information

The ^{1}H, $^{13}C\{^{1}H\}$ and ^{19}F NMR spectra were recorded on a Bruker Avance III 600 spectrometer using the solvent signal as a reference. Assignments of signals in ^{13}C NMR spectra were made on the basis of HMQC experiments. The IR spectra were measured using a NEXUS FT-IR spectrophotometer. The ESI-MS spectra were obtained using a Varian 500 MS LC Ion Trap spectrometer. Optical rotation was measured on a Perkin-Elmer 241 MC polarimeter for λ = 589 nm in $CHCl_3$. Melting points were determined in capillary on a Melt-Temp II apparatus.

4.2. Materials

Commercial ethyl acrylate, benzylamine, (*S*)-1-phenylethylamine, *O*-methylhydroxylamine hydrochloride, tetrabutylammonium fluoride (1M, solution in THF), methylmagnesium bromide (3M, solution in THF) and trimethylaluminium were purchased from Sigma-Aldrich and (trifluoromethyl)trimethylsilane from Fluorochem. Aziridinyl carboxylates **1** and the corresponding Weinreb amides **2** were prepared according to the method described in ref. [1d]. Benzaldehyde was distilled prior to use. Solvents used in the study (THF, DME, toluene, and benzene) were dried over sodium, CH_2Cl_2 over sodium hydride, and freshly distilled prior to use. The aziridine amides **2a**, (*S,S*)- and (*S,R*)-**2b** were prepared according to known procedures [8,9].

4.3. Reactions of Weinreb amides with Grignard reagents – general procedure

A Weinreb amide **2** (10 mmol) was dissolved in an anhydrous solvent (15 ml) (THF for reactions with MeMgBr or Et_2O for reactions with PhMgBr) and placed in a three-neck round-bottom flask equipped with a mechanic stirrer. In each reaction, a three-fold molar amount of Grignard reagent was used. The reaction flask was cooled to –78 °C in a cooling bath and subsequently a solution of Grignard reagent was added drop-wise. After 0.5 h, the cooling bath was removed and the solution was slowly warmed to room

temperature. The progress of the reaction was monitored by TLC (AcOEt). The reaction was quenched with saturated aqueous solution of NaCl and extracted with Et_2O (3 × 50 ml), the combined organic layers were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Products were purified by column chromatography on silica gel with AcOEt/hexane (1:9) (for compounds **3a**,**c**,**e**) or AcOEt/petroleum ether (2:8) (for compounds **3b**,**d**,**f**) as eluent.

2-Acetyl-1-benzylaziridine (**3a**) [10]. Yield: 0.77 g (44%). Brown oil. Spectroscopic data in agreement with ref. [10]. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.83 (dd, 1H, $^2J_{H,H}$ = 2.5 Hz, $^3J_{H,H}$ = 5.2 Hz, $H_{(B)}C(3)$), 2.07 (s, 3H, CH_3CO), 2.23-2.24 (m, 2H, $H_{(A)}C(3)$, HC(2)), 3.47, 3.57 (AB-system, 2H, $^2J_{H,H}$ = 13.2 Hz, C**H**$_2$Ph), 7.30–7.34 (m, 5 arom. CH).

2-Benzoyl-1-benzylaziridine (**3b**) [8,11]. Yield: 1.31 g (55%). Brown oil. Spectroscopic data in agreement with ref. [11]. ^{1}H-NMR ($CDCl_3$, 600 MHz): δ 1.93 (dd, 1H, $^2J_{H,H}$ = 1.3 Hz, $^3J_{H,H}$ = 6.4 Hz, $H_{(B)}C(3)$), 2.44 (dd, 1H, $^2J_{H,H}$ = 1.4 Hz, $^3J_{H,H}$ = 3.2 Hz, $H_{(A)}C(3)$), 2.99 (dd, 1H, $^2J_{H,H}$ = 3.2 Hz, $^3J_{H,H}$ = 6.5 Hz, HC(2)), 3.54, 3.83 (AB system, 2H, $^2J_{H,H}$ = 13.8 Hz, C**H**$_2$Ph), 7.26–7.56 and 7.92–7.94 (2m, 10 arom. CH).

2-Acetyl-1'S,2S)-1-(1'-phenylethyl)aziridine ((*S,S*)-**3c**) [1d]. Yield: 0.54 g (28%). Brown oil. ^{1}H-NMR ($CDCl_3$, 600 MHz): δ 1.42 (d, $^3J_{H,H}$ = 6.6 Hz, 3H, PhCHC**H**$_3$), 1.66 (d, $^3J_{H,H}$ = 6.8 Hz, 1H, $H_{(B)}C(3)$), 2.06 (d, $^3J_{H,H}$ = 2.9 Hz, 1H, $H_{(A)}C(3)$), 2.08 (s, 3H, CH_3CO), 2.21 (dd, $^3J_{H,H}$ = 3.1 Hz, $^3J_{H,H}$ = 6.8 Hz, 1H, HC(2)), 2.55 (q, 1H, $^3J_{H,H}$ = 6.5 Hz, PhC**H**CH_3), 7.25–7.39 (m, 5 arom. CH). ^{13}C-NMR ($CDCl_3$, 150 MHz): δ 23.3 (**C**H_3), 24.6 (PhCH**C**H_3), 34.2 (CH_2), 45.8 (CH), 69.5 (Ph**C**HCH_3); 126.7, 127.3, 128.4 (5 arom. CH), 143.9 (1 arom. **C**), 207.6 (**C**=O). IR (KBr): *v* 3027*m*, 2966*s*, 1701*vs* (C=O), 1583*m*, 1494*m*, 1352*s*, 1264*s*, 700*vs* cm^{-1}. HR-ESI-MS (MeOH+NaI): 212.10454 (212.10459 calcd. for $C_{12}H_{15}NaNO$, [*M*+Na]$^+$). $[\alpha]^{25}_D$ = –129.1 (*c* = 0.5; $CHCl_3$).

2-Benzoyl-(1'S,2S)-1-(1'-phenylethyl)aziridine ((*S,S*)-**3d**) [1d]. Yield: 0.86 g (33%). Brown oil. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.52 (d, 3H, $^3J_{H,H}$ = 6.5 Hz, PhCHC**H**$_3$), 1.80 (dd, 1H, $^2J_{H,H}$ = 1.4 Hz, $^3J_{H,H}$ = 6.5 Hz, $H_{(B)}C(3)$), 2.28 (dd, 1H, $^2J_{H,H}$ = 1.3 Hz, $^3J_{H,H}$ = 3.1 Hz, $H_{(A)}C(3)$), 2.27 (q, 1H, $^3J_{H,H}$ = 6.6 Hz, PhC**H**CH_3), 3.05 (dd, 1H, $^3J_{H,H}$ = 3.1 Hz,

$^{3}J_{H,H}$ = 6.5 Hz, HC(2)), 7.28–7.61 and 8.12–8.13 (m, 10 arom. CH). ^{13}C-NMR ($CDCl_3$, 150 MHz): δ 23.5 (**C**H_3), 36.1 (**C**H_2), 42.0 (**C**H), 70.3 (Ph**C**HCH_3); 127.0, 127.3, 128.4, 128.5, 128.7, 133.2 (10 arom. CH), 136.9, 143.6 (2 arom. **C**), 196.2 (**C**=O). **IR** (KBr): *v* 3032*m*, 2973*s*, 1677*vs* (C=O), 1597*m*, 1447*s*, 1230*vs*, 1013*s*, 697*vs* cm^{-1}. HR-ESI-MS (MeOH+NaI): 274.12032 (274.12024 calcd. for $C_{17}H_{17}NNaO$, [*M*+Na]$^+$). $[\alpha]^{25}_D$ = –65.5 (*c* = 0.5; $CHCl_3$).

2-Benzoyl-(1'S,2R)-1-(1'-phenylethyl)aziridine ((*S,R*)-**3e**) [12]. Spectroscopic data in agreement with ref. [12]. Yield: 1.08 g (42%). Brown oil. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.56 (d, 3H, $^{3}J_{H,H}$ = 6.5 Hz, PhCHC**H**$_3$), 1.97 (dd, 1H, $^{2}J_{H,H}$ = 1.4 Hz, $^{3}J_{H,H}$ = 6.4 Hz, $H_{(B)}$C(3)), 2.59 (dd, 1H, $^{2}J_{H,H}$ = 1.4 Hz, $^{3}J_{H,H}$ = 3.2 Hz, $H_{(A)}$C(3)), 2.74 (q, 1H, $^{3}J_{H,H}$ = 6.6 Hz, PhC**H**CH_3), 2.91 (dd, $^{3}J_{H,H}$ = 3.1 Hz, $^{3}J_{H,H}$ = 6.4 Hz, HC(2)), 7.25–7.40 (m, 5 arom. CH). $[\alpha]^{25}_D$ = +23.2 (*c* = 0.5; $CHCl_3$).

Reactions of aziridinyl ketones with (trifluoromethyl)trimethylsilane – general procedure

A solution of the corresponding aziridinyl ketone **3** (1.0 mmol) in anhydrous DME (1.0 ml), was placed in a dry, two-necked flask, equipped with a tube filled with $CaCl_2$. Next, a catalytic amount of freshly dried CsF was added, and subsequently, (trifluoromethyl)trimethylsilane (230 mg, 1.6 mmol) was added dropwise. The mixture was stirred magnetically for *ca*. 1 h, and the progress of the reaction was monitored by TLC (CH_2Cl_2). Next, the reaction was quenched with a sat. aqueous solution of NaCl (10 ml), and the mixture was extracted with CH_2Cl_2 (3 × 15 ml). The organic layers were combined and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated. The diastereoisomeric products were purified and separated by column chromatography on silica gel by using a mixture of hexane/AcOEt (4.9:0.1) for compounds **4a**,**b** and **4a'**,**b'** or CH_2Cl_2/pentane (1:4) for derivatives **4c**-**e** and **4c'**-**e'**.

Desilylation of trimethylsilyl ethers with tetrabutylammonium fluoride (TBAF) – general procedure

The corresponding silyl ether **4** (1.0 mmol) was dissolved in anhydrous THF, and a solution of TBAF (1.1 ml, 1.1 mmol) was added dropwise while the reaction flask was cooled in an ice-bath. The progress of the reaction was monitored by TLC. Subsequently, the reaction was quenched with a sat. aqueous solution of NaCl (10 ml),

and the obtained mixture was extracted with CH_2Cl_2 (3×15 ml). The organic layers were combined and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated, and the crude products were purified by microdistillation (external temperature 150–160 °C, p = 0.1 hPa, Kugelrohr).

Spectroscopic data are given for the diastereoisomers of the desilylated products.

1-Benzyl-2-[2,2,2-trifluoro-1-methyl-1-(trimethylsilyloxy)ethyl]aziridine (fast, **4a**). Yield: 75 mg (10%), colorless oil (contaminated by ca. 9% of **4a'**).

2-(1-Benzylaziridin-2-yl)-1,1,1-trifluoropropan-2-ol (**5a**). Yield: 100 mg (41%). Colourless crystals, m.p. 68–72 °C (contaminated by ca. 6% of **5a'**). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.14 (s, 3H, CH_3), 1.62 (d, 1H, C**H**$_2$CH, $^3J_{H,H}$ = 6.6 Hz), 1.77 (dd, 1H, C**H**$_2$CH, $^3J_{H,H}$ = 3.0 Hz, $^3J_{H,H}$ = 6.6 Hz), 2.13 (d, 1H, CH_2C**H**, $^3J_{H,H}$ = 3.0 Hz), 3.25 (s, 1H, OH), 3.24, 3.32 (AB system, 2H, C**H**$_2$Ph, $^2J_{H,H}$ = 13.2 Hz), 7.30–7.37 (m, 5 arom. CH). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 22.0 (**C**H_3), 30.6 (**C**H_2CH), 39.9 (CH_2**C**H), 63.5 (**C**H_2Ph), 70.0 (q, COH, $^2J_{C,F}$ = 28.5 Hz), 126.7 (q, **C**F_3, $^1J_{C,F}$ = 282.2 Hz), 127.7, 128.6, 128.6 (5 arom. CH), 138.0 (1 arom. C). ^{19}F NMR ($CDCl_3$, 565 MHz): δ –81.0 (s, CF_3). IR (KBr) ν 3422m (O–H), 3067m, 3038m, 3004m, 2952m, 2897m, 2839m, 1499m, 1455m, 1165s (C–F), 1152s (C–F), 1123s (C–F), 1084m, 1027m, 990m, 746s, 701s cm^{-1}. ESI-MS: 245.0 (M^+, 100), 244.3 ([M–1]$^+$, 90), 243.2 ([M–2]$^+$, 38); HR-ESI-MS (MeOH+NaI): 246.10995 (246.11003 calcd. for $C_{12}H_{15}F_3NO$, [*M*+H]$^+$).

1-Benzyl-2-[2,2,2-trifluoro-1-methyl-2-(trimethylsilyloxy)ethyl]aziridine (slow, **4a'**). Yield: 121 mg (49%), colorless oil.

2-(1-Benzylaziridin-2-yl)-1,1,1-trifluoropropan-2-ol (**5a'**). Yield: 110 mg (45%). Colourless oil. ^{1}H-NMR ($CDCl_3$, 600 MHz): δ 1.30 (s, 3H, CH_3), 1.48 (d, 1H, C**H**$_2$CH, $^3J_{H,H}$ = 6.6 Hz), 1.79 (d, 1H, C**H**$_2$CH, $^3J_{H,H}$ = 3.6 Hz), 2.00 (dd, 1H, CH_2C**H**, $^3J_{H,H}$ = 3.6 Hz, $^3J_{H,H}$ = 6.6 Hz), 3.22, 3.96 (AB system, 2H, C**H**$_2$Ph, $^2J_{H,H}$ = 13.2 Hz), 3.65 (s, 1H, OH), 7.28–7.34 (m, 5 arom. CH). ^{13}C-NMR ($CDCl_3$, 150 MHz): δ 18.5 (CH_3), 27.6 (**C**H_2CH), 39.4 (CH_2**C**H), 62.1 (**C**H_2Ph), 69.4 (q, COH, $^2J_{C,F}$ = 27.7 Hz), 126.2 (q, CF_3, $^1J_{C,F}$ = 284.5 Hz), 127.5, 128.4, 128.4 (5 arom. CH), 137.6 (1 arom **C**). ^{19}F-NMR ($CDCl_3$, 565 MHz): δ –82.5 (s, CF_3). IR (film): *v* 3392*w* (O–H), 3089*m*, 3065*m*, 3032*m*,

2997*m*, 2947*m*, 1497*m*, 1455*m*, 1184*s* (C–F), 1151*s* (C–F), 1106*s* (C–F), 1072*m*, 1029*m*, 1007*m*, 897*m*, 742*s*, 698*s* cm^{-1}. ESI-MS: 244.9 (M^+, 100), 243.0 ([*M*–2]$^+$, 20); HR-ESI-MS (MeOH+NaI): 246.11013 (246.11003 calcd. for $C_{12}H_{15}F_3NO$, [*M*+H]$^+$).

1-Benzyl-2-[2,2,2-trifluoro-1-phenyl-1-(trimethylsilyloxy)ethyl]aziridine (fast, **4b**). Yield: 77 mg (20%). Colourless oil.

1-(1-Benzylaziridin-2-yl)-2,2,2-trifluoro-1-phenylethanol (**5b**). Yield: 101 mg (33%). Colourless crystals, m.p. 77–79 °C. ^{1}H-NMR ($CDCl_3$, 600 MHz): δ 1.73 (d, 1H, C**H**$_2$CH, $^3J_{H,H}$ = 6.0 Hz), 2.29 (d, 1H, C**H**$_2$CH, $^3J_{H,H}$ = 3.0 Hz), 2.40 (dd, 1H, CH_2C**H**, $^3J_{H,H}$ = 3.0 Hz, $^3J_{H,H}$ = 6.0 Hz), 3.42, 3.55 (AB-system, $^2J_{H,H}$ = 12.6 Hz, 2H, C**H**$_2$Ph), 3.88 (s, 1H, OH), 7.03–7.05, 7.12–7.15, 7.30–7.32, 7.55–7.57 (4m, 10 arom. CH). ^{13}C-NMR ($CDCl_3$, 150 MHz): δ 30.4 (**C**H_2CH), 40.8 (CH_2**C**H), 62.7 (**C**H_2Ph), 73.0 (q, COH, $^2J_{C,F}$ = 28.4 Hz), 125.1 (q, CF_3, $^1J_{C,F}$ = 283.2 Hz), 126.3, 127.3, 127.9, 128.2, 128.3, 128.4 (10 arom. CH), 137.4, 138.5 (2 arom. C). ^{19}F-NMR ($CDCl_3$, 565 MHz): δ –77.2 (s, CF_3). IR (KBr) ν 3239*m* (O–H), 3111*m*, 3090*m*, 3072*m*, 3030*m*, 3007*m*, 2963*m*, 2924*m*, 2869*m*, 1497*m*, 1456*m*, 1191*s* (C–F), 1171*s* (C–F), 1148*s* (C–F), 1085*m*, 1072*m*, 1038*m*, 904*m*, 743*s*, 703*s* cm^{-1}. ESI-MS *m*/*z* 306.3 ([*M*–1]$^+$, 100), 305.2 ([*M*–2]$^+$), 60]. HR-ESI-MS (MeOH+NaI): 308.12579 (308.12568 calcd. for $C_{17}H_{17}F_3NO$, [*M*+H]$^+$).

1-Benzyl-2-[2,2,2-trifluoro-1-phenyl-1-(trimethylsilyloxy)ethyl]aziridine (slow, **4b'**). Yield: 167 mg (44%). Colourless oil.

1-(1-Benzylaziridin-2-yl)-2,2,2-trifluoro-1-phenylethanol (**5b'**). Yield: 74 mg (24%). Colourless crystals, m.p. 103–106 ºC (hexane/CH_2Cl_2). ^{1}H-NMR ($CDCl_3$, 600 MHz): δ 1.52 (d, 1H, C**H**$_2$CH, $^3J_{H,H}$ = 6.6 Hz), 1.60 (d, 1H, C**H**$_2$CH, $^3J_{H,H}$ = 3.6 Hz,), 2.56 (dd, 1H, CH_2C**H**, $^3J_{H,H}$ = 3.6 Hz, $^3J_{H,H}$ = 6.6 Hz), 3.34, 4.08 (AB-system, $^2J_{H,H}$ = 13.2 Hz, 2H, C**H**$_2$Ph), 4.44 (s, 1H, OH), 7.29–7.39, 7.57–7.58 (2m, 10 arom. CH). ^{13}C-NMR ($CDCl_3$, 150 MHz): δ 28.5 (**C**H_2CH), 39.6 (CH_2**C**H), 61.9 (**C**H_2Ph), 72.2 (q, COH, $^2J_{C,F}$ = 28.2 Hz), 125.5 (q, CF_3, $^1J_{C,F}$ = 285.5 Hz), 126.3, 127.6, 128.1, 128.4, 128.5, 128.6 (10 arom. CH), 136.5, 137.4 (2 arom. C). ^{19}F-NMR ($CDCl_3$, 565 MHz): δ –79.9 (s, CF_3). IR (KBr) *v* 3241*m* (O–H), 3087*m*, 3073*m*, 3028*m*, 3008*m*, 2997*m*, 2961*m*, 2927*m*, 1496*m*, 1454*m*, 1181*s* (C–F), 1160*s* (C–F), 1148*s* (C–F), 1088*m*, 1072*m*, 1036*m*, 907*m*,

745*s*, 697*s* cm^{-1}. ESI-MS: *m/z* 305.6 ($[M-1]^+$, 100), 305.2 ($[M-2]^+$, 75); HR-ESI-MS (MeOH+NaI): 308.12542 (308.12568 calcd. for $C_{17}H_{17}F_3NO$, $[M+H]^+$).

(1"S,2'S,2S)-1-(1-Phenylethyl)-2-[2,2,2-trifluoro-1-methyl-1-(trimethylsilyloxy)ethyl]aziridine (fast, $R_f = 0.22$, **4c**). Yield: 104 mg (31%). Colourless oil.

(1"S,2'S,2S)-2-[1-(1-Phenylethyl)aziridin-2-yl]-1,1,1-trifluoropropan-2-ol (**5c**). Yield: 196 mg (71%). Colourless crystals, m.p. 34–37 °C. ^{1}H-NMR ($CDCl_3$, 600 MHz): δ 1.45-1.47 (m, 3H+1H, C**H**$_3$CHPh, C**H**$_2$CH), 1.56 (d, $^3J_{H,H}$ = 1.0 Hz, 3H, CH_3), 1.85 (dd, $^3J_{H,H}$=3.3 Hz, 1H, C**H**$_2$CH), 2.75 (q, $^3J_{H,H}$ = 6.5 Hz, 1H, CH_3C**H**Ph), 3.28 (s, 1H, OH), 7.28–7.30, 7.32–7.34 (2m, 5 arom. CH). ^{13}C-NMR ($CDCl_3$, 150 MHz): δ 22.5 (**C**H_3CHPh), 23.6 (CH_3), 29.8 (**C**H_2CH), 40.8 (CH_2**C**H), 68.1 (CH_3**C**HPh), 70.0 (d, $^2J_{C,F}$ = 28,4 Hz, COH), 126.6, 127.4, 128.5 (5 arom. **C**H), 125.8 (q, $^1J_{C,F}$ = 282.1 Hz, CF_3), 143.6 (1 arom. C). ^{19}F-NMR ($CDCl_3$, 565 MHz): δ –80.83 (s, CF_3). IR (KBr): δ 3416 (O–H), 2985*m*, 2979*m*, 1456*m*, 1383*s*, 1200*m*, 1164*s* (C–F), 1151*s* (C–F), 1102*m*, 1078*m*, 703*s* cm^{-1}. ESI-MS: 282 ($[M^+$+Na$]^+$, 27), 260 ($[M+1]^+$, 100); HR-ESI-MS: 260.12589 (260.12568 calcd. for $C_{13}H_{17}F_3NO$, $[M+H]^+$). $[\alpha]^{25}_D$ = –33.0 (*c* = 0.5, $CHCl_3$).

(1"S,2'S,2R)-1-[(1-Phenylethyl)-2-[2,2,2-trifluoro-1-methyl-1-(trimethylsilyloxy)ethyl]aziridine (slow, $R_f = 0.09$, **4c'**). This compound was isolated as a minor product (ca. 18% yield) contaminated with substantial amounts of **4c** and has not been used for desilylation.

(1"S,2'S,1S)-1-(1-Phenylethyl)-2-[2,2,2-trifluoro-1-phenyl-1-(trimethylsilyloxy)ethyl]aziridine (fast, **4d**). Yield: 134 mg (34%). Colourless semi-solid.

(1"S,2'S,1S)-1-[1-(1-Phenylethyl)aziridin-2-yl)-2,2,2-trifluoro-1-phenylethanol (**5d**). Yield: 96 mg (28%). Colourless solid, m.p. 84–86°C. ^{1}H-NMR ($CDCl_3$, 600 MHz): δ 0.83 (d, $^3J_{H,H}$ = 6.0 Hz, 3H, C**H**$_3$CHPh), 1.60 (d, $^3J_{H,H}$ = 6.6 Hz, 1H, C**H**$_2$CH), 2.15 (d, $^3J_{H,H}$ = 3.0 Hz, 1H, C**H**$_2$CH), 2.38 (dd, $^3J_{H,H}$ = 3.0 Hz, $^3J_{H,H}$ = 6.6 Hz, 1H, CH_2C**H**), 2.71 (q, $^3J_{H,H}$ = 6.0 Hz, 1H, CH_3C**H**Ph), 4.11 (s, 1H, OH), 7.25–7.28, 7.31–7.34, 7.38–7.41,

7.43–7.47, 7.74–7.76 (5m, 10 arom. CH). ^{13}C-NMR ($CDCl_3$, 150 MHz): δ 23.1 (**C**H_3CHPh), 30.0 (**C**H_2CH), 42.2 (CH_2**C**H), 67.7 (CH_3**C**HPh), 73.0 (q, $^2J_{C,F}$ = 28.8 Hz, COH), 125.2 (q, $^1J_{C,F}$ = 282.9 Hz, CF_3), 126.4, 126.5, 127.4, 128.3, 128.4, 128.6 (10 arom. CH), 138.9, 143.4 (2 arom. C). ^{19}F-NMR ($CDCl_3$, 565 MHz): δ –76.9 (s, CF_3). IR (KBr) *v* 3383*m*, 3063*m*, 3025*m*, 2966*m*, 2925*m*, 2869*m*, 1496*m*, 1456*m*, 1192*s* (C–F), 1173*s* (C–F), 1150*s* (C–F), 1096*m*, 1071*m*, 1024*m*, 757*s*, 698*s* cm^{-1}. ESI-MS: 319.7 ([*M*–1]$^+$, 95], 318.6 ([*M*–2]$^+$, 100); HR-ESI-MS (MeOH+NaI): 322.14111 (322.14133 calcd for $C_{18}H_{19}F_3NO$, [*M*+H]$^+$). $[\alpha]^{25}_D$ = –30.5 (*c* = 1.0, $CHCl_3$).

(1"S,2'S,1R)-1-(1-Phenylethyl)-2-[2,2,2-trifluoro-1-phenyl-1-(trimethylsilyloxy)ethyl]aziridine (slow, **4d'**)**.** Yield: 118 mg (30%). Colourless oil.

(1"S,2'S,1R)-1-[1-(1-Phenylethyl)aziridin-2-yl)-2,2,2-trifluoro-1-phenylethanol (**5d'**). Yield: 106 mg (33%). Colourless crystals, m.p. 98–104 °C. ^{1}H-NMR ($CDCl_3$, 600 MHz): δ 1.36 (d, $^3J_{H,H}$ = 6.6 Hz, 1H, C**H**$_2$CH), 1.44 (d, $^3J_{H,H}$ = 3.0 Hz, 1H, C**H**$_2$CH), 1.51 (d, $^3J_{H,H}$ = 6.6 Hz, 3H, C**H**$_3$CHPh), 2.60 (dd, $^3J_{H,H}$ = 3.0 Hz, $^3J_{H,H}$ = 6.6 Hz, 1H, CH_2C**H**), 2.92 (q, $^3J_{H,H}$ = 6.6 Hz, 1H, CH_3C**H**Ph), 4.45 (s, 1H, OH), 7.27–7.29, 7.33–7.39, 7.58–7.90 (3m, 10 arom. CH). ^{13}C-NMR ($CDCl_3$, 150 MHz): δ 22.9 (**C**H_3CHPh), 28.1 (**C**H_2CH), 40.6 (CH_2**C**H), 68.0 (CH_3**C**HPh), 72.5 (q, $^2J_{C,F}$ = 27.75 Hz, COH), 125.6 (q, $^1J_{C,F}$ = 261 Hz, CF_3), 126.1, 126.7, 127.4, 128.2, 128.5, 128.5 (10 arom. CH), 136.7, 143.6 (2 arom. C). ^{19}F-NMR ($CDCl_3$, 565 MHz): δ –78.5 (s, CF_3). IR (KBr) *v* 3281*w* (O–H), 3088*m*, 3063*m*, 3034*m*, 2977*m*, 2930*m*, 2872*m*, 1495*m*, 1452*s*, 1189*s* (C–F), 1159*s* (C–F), 1151*s* (C–F), 1073*m*, 1037*m*, 1016*m*, 905*m*, 758*s*, 700*s* cm^{-1}. ESI-MS: *m*/*z* 320.0 ([*M*–1]$^+$, 60), 319.2 ([*M*–2]$^+$, 100); HR-ESI-MS: (MeOH+NaI): 322.14121 (322.14133 calcd for $C_{18}H_{19}F_3NO$, [*M*+H]$^+$). $[\alpha]_D^{25}$ = +12.1 (*c* = 2.3, $CHCl_3$).

(1"S,2'R,1S)-1-(1-Phenylethyl)-2-[2,2,2-trifluoro-1-phenyl-1-(trimethylsilyloxy)ethyl]aziridine (fast, **4e**). Yield: 163 mg (44%). Colourless oil.

(1",2'R,1S)-1-[1-(1-Phenylethyl)aziridin-2-yl)-2,2,2-trifluoro-1-phenylethanol (**5e**). Yield: 282 mg (88%). Colourless crystals, m.p. 72–73°C. ^{1}H-NMR ($CDCl_3$, 600 MHz): δ 1.37 (d, $^3J_{H,H}$ = 6.6 Hz, 3H, C**H**$_3$CHPh), 1.69 (d, $^3J_{H,H}$ = 6.1 Hz, 1H, C**H**$_2$CH), 2.28 (dd, $^2J_{H,H}$ = 3.3 Hz, $^3J_{H,H}$ = 6.1 Hz, 1H, CH_2C**H**), 2.31 (dd, $^2J_{H,H}$ = 1.0 Hz, $^3J_{H,H}$ = 3.3

Hz, 1H, C**H**$_2$CH), 2.71 (q, $^3J_{H,H}$ = 6.6 Hz, 1H, CH$_3$C**H**Ph), 3.84 (s, 1H, OH), 6.85–6.96, 7.04–7.10, 7.26–7.28 (3m, 10 arom. CH). ^{13}C-NMR ($CDCl_3$, 150 MHz): δ 22.7 (**C**H$_3$CHPh), 30.2 (**C**H$_2$CH), 39.8 (**C**H), 68.6 (CH$_3$**C**HPh), 72.9 (q, $^2J_{C,F}$ = 28.5 Hz, COH), 125.1 (d, $^1J_{C,F}$ = 283.5 Hz, CF_3), 126.1, 126.4, 127.1, 127.73, 127.9, 128.0 (10 arom. CH), 138.1, 142.4 (2 arom. C). ^{19}F-NMR ($CDCl_3$, 565 MHz): δ –77.4 (s, CF_3). IR (KBr): *v* 3443*m* (O–H), 3088*m*, 3063*m*, 3031*m*, 2983*m*, 2963*m*, 2925*m*, 2867*m*, 1495*m*, 1450*m*, 1256*s* (C–F), 1167*s* (C–F), 1157*s* (C–F), 1099*m*, 1070*m*, 1017*m*, 756*s*, 699*s* cm^{-1}. ESI-MS: 322 ([*M*+1]$^+$, 100), 344 ([*M*+Na]$^+$, 7.5). HR-ESI-MS (MeOH+NaI): 322.14174 (322.14133 calcd for $C_{18}H_{19}F_3NO$, [*M*+H]$^+$). $[\alpha]^{25}_D$ = –50.0 (*c* = 1.0, $CHCl_3$).

(1"S,2'R,1R)-1-(1-Phenylethyl)-2-[2,2,2-trifluoro-1-phenyl-1-(trimethylsilyloxy)ethyl]aziridine (slow, **4e'**). This compound was isolated as a minor product (ca. 2% yield) contaminated with substantial amounts of **4e** and has not been used for desilylation.

4.6. X-Ray crystal-structure determination of **5c**

All measurements were performed on a Nonius KappaCCD area-detector diffractometer [20] using graphite-monochromated MoK_α radiation (λ 0.71073 Å) and an Oxford Cryosystems Cryostream 700 cooler. The data collection and refinement parameters are given below [21] and a view of the molecule is shown in Figure 1. Data reduction was performed with HKL Denzo and Scalepack [22]. The intensities were corrected for Lorentz and polarization effects, but not for absorption. Equivalent reflections were merged. The structure was solved by direct methods using SHELXS97 [23], which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically. The hydroxy H-atom was placed in the position indicated by a difference electron density map and its position was allowed to refine together with an isotropic displacement parameter. All remaining H-atoms were placed in geometrically calculated positions and refined by using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2U_{eq} of its parent C-atom (1.5U_{eq} for the methyl groups). The refinement of the structure was carried out on F^2 using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. A correction for secondary extinction was applied. One reflection, whose intensity was considered to be an extreme outlier, was omitted from

the final refinement. Neutral atom scattering factors for non-H-atoms were taken from ref. [24], and the scattering factors for H-atoms were taken from ref. [25] Anomalous dispersion effects were included in F_c [26]; the values for f' and f'' were those of ref. [27]. The values of the mass attenuation coefficients are those of ref. [28]. All calculations were performed using the *SHELXL97* [23] program.

Crystal data for **5c**: $C_{13}H_{16}F_3NO$, M = 259.27, crystallised from hexane, colourless, prism, crystal dimensions 0.17 × 0.23 × 0.30 mm, orthorhombic, space group $P2_12_12_1$, Z = 4, reflections for cell determination 1728, 2θ range for cell determination 4 – 55°, a = 10.3719(2) Å, b = 14.9112(3) Å, c = 8.4315(2) Å, V = 1303.99(9) Å^3, T = 160(1) K, D_X = 1.321 g·cm^{-3}, μ(MoK_α) = 0.112 mm^{-1}, scan type ϕ and ω, $2\theta_{(max)}$ = 55°, total reflections measured 16513, symmetry independent reflections 1720, reflections with $I > 2\sigma(I)$ 1537, reflections used in refinement 1719, parameters refined 170; $R(F)$ [$I > 2\sigma(I)$ reflections] = 0.0350, $wR(F^2)$ [all data] = 0.0902 ($w = [\sigma^2(F_o^2)+ (0.0497P)^2+0.1876P]^{-1}$, where $P = (F_o^2+2F_c^2)/3$), goodness of fit 1.049, final Δ_{max}/σ 0.002, $\Delta\rho$ (max; min) = 0.19; –0.16 e Å^{-3}, secondary extinction coefficient = 0.023(5).

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